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2018

## Systematic review and meta-analysis on efficacy of Fostera PRRSV Modified Live Virus vaccine studies in growing pigs

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### Recommended Citation

Rawal, Gaurav; Angulo, Jose; Linhares, Daniel C. L.; and O'Connor, Annette M., "Systematic review and meta-analysis on efficacy of Fostera PRRSV Modified Live Virus vaccine studies in growing pigs" (2018). *Veterinary Diagnostic and Production Animal Medicine Reports*. 9.

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# Systematic review and meta-analysis on efficacy of Fosterera PRRSV Modified Live Virus vaccine studies in growing pigs

## Abstract

Porcine reproductive and respiratory syndrome virus (PRRSV) is one of the most economically important health challenges that currently exists in the global swine industry. PRRSV is an enveloped, single-stranded, positive-sense RNA virus belonging to genus Arterivirus. A PRRSV infection is clinically characterized by reproductive failure in sows and/or respiratory disease in growing pigs, causing significant economic losses (Zimmerman et al., 2012). RNA viruses have relatively high mutation rates compared to DNA viruses, mainly due to the low fidelity of viral RNA-dependent RNA polymerases (Arnold et al., 2005; Vignuzzi et al., 2008). This rapid high mutation rate usually leads to the generation of genetically and antigenically variable virus strains in the field, which can hinder the development of effective vaccines. PRRSV is currently classified into two distinct genotypes, type 1 and type 2 which differs significantly in term of their clinical, and genetic properties (Kapur et al., 1996; Labarque et al., 2004; Nelson et al., 1993). Within type 2, it has been proposed a further subdivision into 9 genetic lineages (Shi et al., 2010). The extensive heterogeneity of PRRSV presents challenges for the efficacy vaccines, which are currently based on a single virus strain. Consequently, the current commercially vaccines confer partial cross-protection against heterologous PRRSV strains (Kimman et al., 2009; Li et al., 2014; Murtaugh and Genzow, 2011), which is sufficient to significantly decrease duration and magnitude of viremia, shedding, and lung lesions. In previous cross-protection studies, type 2 PRRSV modified live vaccine have not been effective when applied to control pigs against type 1 PRRSV (Labarque et al., 2003; van Woensel et al., 1998; Labarque et al., 2000). Cross-protection discoursed by type 2 PRRSV vaccine against type 1 PRRSV is an important clinical issue in many Asian countries because of the emergence of type 1 PRRSV (Chen et al., 2011; Nam et al., 2009; Thanawongnuwech et al., 2004). A modified live type 2 PRRSV vaccine (Fosterera PRRS, Zoetis, Parsippany, NJ, USA) was introduced in the US in 2012, and is profess to be efficacious to protect pigs against heterologous type 2 PRRSV challenge (Park et al., 2014), and has been licensed to produce better cross-protection against heterologous PRRSV challenge. Fosterera PRRS is an attenuated PRRSV vaccine, passaged first on pig kidney cells engineered to constitutively express the porcine CD163 PRRS receptor, then on baby hamster kidney cells that were also engineered to express porcine CD163. The commercial modified live PRRS vaccines were attenuated by passage on African green monkey kidney cells (cell line MA-104 and derivatives), which inappropriately express the macrophage-specific CD163 PRRS receptor. Adaptation of the virus to use the monkey CD163 receptor contributes to the observed attenuation phenotype of at least some of these vaccines, namely a reduced ability of the vaccine virus to infect the host target cell, primary porcine alveolar macrophages (Pearce et al., 2014). In contrast, the Fosterera PRRSV is passaged only on cells expressing porcine CD163, and thus potentially maintaining its ability to replicate to high titer on primary porcine alveolar macrophages. This fundamental difference in attenuation may play a role in the dynamics of viremia in pigs, following challenge with PRRS viruses from genotypes 1 (Charoenchanikran et al., 2016; Choi et al., 2016; Do et al., 2015; Park et al., 2015, 2014; Savard et al., 2016; Tian et al., 2015).

## Disciplines

Agricultural Economics | Large or Food Animal and Equine Medicine | Veterinary Pathology and Pathobiology | Veterinary Preventive Medicine, Epidemiology, and Public Health

**Title**

Systematic review and meta-analysis on efficacy of Foster PRRSV Modified Live Virus vaccine studies in growing pigs.

**Registration**

**APPROVED**

By O'Connor, Annette M [VDPAM] at 8:09 am, Apr 10, 2018

NA



Gaurav Rawal, April 10, 2018 at 9:03 am

**Authors**



Daniel Linhares April 11, 2018 at 15:34h

Gaurav Rawal<sup>1</sup>, grawal@iastate.edu; Jose Angulo<sup>2</sup>, jose.angulo@zoetis.com; Daniel C.L.

Linhares<sup>1</sup>, linhares@iastate.edu; A.M. O'Connor<sup>1,3</sup>, oconnor@iastate.edu;

<sup>1</sup> Department of Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA, USA<sup>Text</sup>

<sup>2</sup> Zoetis, Managing Veterinarian, PRRS Specialist. Pork Technical Services, North Carolina, USA

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G. Rawal contributed the question and the development of all parts of the protocol. G. Rawal assessed the adequacy of the terms for identifying relevant challenge study. J. Angulo contributed to assessing the updating the search, redesign of the screening tools and design of data extraction tools. A. O'Connor and D.C.L. Linhares assess the adequacy of the proposed

systematic review, meta-analysis methods and reviewing of manuscript.

## **Amendments**

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## **Support**

NA

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79    the enrolled pigs, or country where trials were carried out will not be used as an exclusion factor.

80    Intervention

81    Eligible intervention is Fostera modified live PRRSV type 2 vaccine.

82    Comparator

83    Unvaccinated challenged pigs.

84    Outcome

The primary outcome of interest is macroscopic lung lesion mean score, and the secondary outcome of interest are level of viremia ( $\log_{10}$  TCID<sub>50</sub>/mL), duration of viremia and average daily gain (ADG) at different days' post challenge with wild type heterologous PRRSV.

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Eligible studies will be randomized controlled parallel trials that allocate individual level study population of swine. At least one treatment arm i.e. challenged and vaccinated with Foster's PRRSV vaccine (Zoetis, Parsippany, NJ, USA), and a concurrent comparison arm i.e. challenged and unvaccinated. They should have at least one of the three outcomes reported.

#### Information sources:

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108 Search strategy:

109 An example search strategy is listed in Table 1. The search will not be restricted by language but  
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Search Number	Search string	No of Results
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111 Table1. Search Strategy using the ISU Web of Science interface from 2012-2018

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117 many were retrieved by the actual search. We will retain the number of items returned by the  
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119 software will be used to manage literature records and data.



120 Selection process

121 At least two reviewers will independently read all abstracts/summaries identified from the  
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124 relevant, all data will be extracted.

125 The 1<sup>st</sup> level (abstract/title) screening question:

126 1. Does the title or abstract indicate primary research describing a challenge trial for the Foster  
127 MLV PRRSV or treatment in growing pigs?

128 The 2<sup>nd</sup> level (full text) screening questions:

129 1. Is the full text available in English?

130 2. Does the study have at least 2 arms and one is Foster administered per the label and another  
131 is challenged and unvaccinated?

132 3. Does the study contain at least one of the three outcomes or interest: macroscopic lesion mean  
133 score, level of viremia, duration of viremia and/or average daily gain (ADG)?

134 **Data collection process:**

135 Study level information

136 1. What is the study id?

137 2. What was the year of the publication?

138 3. What was the year of study conduct?

139 4. What was the country of trial?

- 140 5. Describe the Age and weight units at enrollment?
- 141 6. What was the gender composition?
- 142 7. What was breed or genetic line?
- 143 8. Number of groups in the design?
- 144 9. Pigs were challenged before or after vaccination?
- 145 10. Time from acquisition to vaccination(days)?
- 146 11. Number of days between vaccination and challenge?
- 147 12. Frequency of vaccination?
- 148 13. Vaccination route(s)?
- 149 14. Challenge route(s)?
- 150 15. Dose of challenge?
- 151 16. Which PRRSV strain was used as inoculum?
- 152 17. Report percentage genetic similarity of challenged strain with Foster vaccine strain?
- 153 18. Days between PRRSV challenge and necropsy?
- 154 19. What outcome was reported?
- 155 20. What is the next outcome you want to report?

156 Arm level information

- 157 1. Number of treatment groups?
- 158 2. What method was used for randomization?
- 159 3. How many pigs were allocated in Foster vaccinated and challenged group?
- 160 4. How many pigs were allocated in unvaccinated and challenged i.e. control group?
- 161 5. How many pigs were allocated in another group?
- 162 6. How many weeks of age, they were vaccinated?

- 163 7. What was the mean macroscopic lung lesion score in Fosterla vaccinated and challenged  
164 group?
- 165 8. What was the mean macroscopic lung lesion score in unvaccinated and challenged  
166 group?
- 167 9. What was the level of viremia in Fosterla vaccinated and challenged group?
- 168 10. What was the level of viremia in unvaccinated and challenged group?
- 169 11. What was the duration of viremia in Fosterla vaccinated and challenged group?
- 170 12. What was the duration of viremia in unvaccinated and challenged group?
- 171 13. What was the mean average daily weight gain in Fosterla vaccinated and challenged  
172 group?
- 173 14. What was the mean average daily weight gain in unvaccinated and challenged group?

#### 174 Data collection process

175 Data extraction will be completed independently by at least two reviewers from all eligible  
176 manuscripts. In the event, same study is obtained from multiple sources (i.e. conference  
177 proceedings and a manuscript from MEDLINE), the different sources will be combined to obtain  
178 the most complete trail description.

#### 179 Data items

#### 180 Source of heterogeneity

181 The source of heterogeneity will be PRRSV challenged strain as inoculum, age of pigs when  
182 they are purchased, source from where they are purchased, breed of pigs, weight of pig before  
183 the start of trial, number of days for acclimation before the start of trial, number of pigs per

184 group, number of groups, challenge dose, route of challenge, individually housed or group  
185 housed.

#### 186 Study level information

187 Country where study was conducted, year of conduct, pig mean age, mean weight, gender  
188 composition, breed or genetic line of pigs involved, duration of study observation period.

#### 189 Arm level information

190 Interventions used in each arm (PRRSV strain, dose, route, duration) total number of pigs in trial  
191 arm, number of events (high lung lesion score) in trial arm at the end of study period, mean lung  
192 lesion score outcome per trial arm, mean score of lung lesion score outcome per trial arm,  
193 pharmaceutical sponsorship of treatment, description of blinding of outcome assessment  
194 included (yes/no), description of use of randomization to group (yes/no), use of systematic  
195 allocation to treatment arm (yes/no), and use of allocation restrictions (blocking by time,  
196 blocking by weight, stratification by severity, stratification by sex).

#### 197 **Outcomes and prioritization**

198 The primary outcome of interest is mean score of macroscopic lung lesions, and secondary  
199 outcomes of interest are level of viremia, duration of viremia and average daily gain (ADG).

#### 200 **Risk of bias in individual studies**

201 The Cochrane Risk of Bias Scale for intervention studies will be used to assess bias for all  
202 outcomes together (macroscopic, magnitude and duration of viremia, and ADG) as these are all  
203 considered objective outcomes (Higgins et al., 2011). The bias domains include selection bias  
204 (sequence generation and allocation concealment), detection bias (outcome assessor blinding),

attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential sources of bias. Two reviewers will be independently assessing all sources of bias as “high risk”, “low risk”, or “unclear”. This information will be used as a source of heterogeneity in the meta-analysis.

## **Data Synthesis**

We propose to conduct a meta-analysis using a pair-wise comparison. The suitability of the dataset for this method will be determined when data has been extracted in consultation with a statistician. Unit of analysis will be handled by exclusion as all studies must have the individual as the unit of allocation. Studies with missing data will be excluded from the meta-analysis and identified as such in the results.

Subgroup analysis will include assessment of factors associated with methodological and clinical heterogeneity. The methodological factors (sponsorship and blinding) will be used to assess the systematic bias between studies where the null hypothesis is the beta estimates of the trial factors equal zero. We expect the potential sources of clinical heterogeneity to be the PRRSV strain, number of pigs per group, number of groups, challenge dose, route of challenge, calculation of outcomes, lung lesion evaluation DPC. We will assess this including these factors as indicator variables in the model where the null hypothesis is the beta estimates of the trial factors equal zero.

If quantitative synthesis is determined to be unfeasible, a systematic narrative synthesis paired with descriptive pairwise forest plots will be produced explaining the characteristics and findings within and between included studies.

## **Meta-bias(es)**

227 To assess publication bias, we will attempt use a selection model based on study size, study  
228 design, estimated effect size, and sponsorship to determine estimates of propensity for  
229 publication (Mavridis et al., 2014). Based on previous reviews, it is unclear how many different  
230 study designs (e.g. active-to-active, placebo-controlled trials, three arm trials) will be observed  
231 and thus publication bias will be difficult to ascertain.

#### 232 **Confidence in cumulative evidence**

233 We will summarize the data using the GRADE approach, with a summary of findings tables and  
234 evidence profiles for the multiple outcomes. All the outcomes are considered important or  
235 critical.

**Title**

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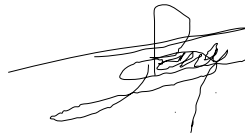
**Registration**

NA

**APPROVED**

By O'Connor, Annette M [VDPAM] at 8:09 am, Apr 10, 2018

**Authors**



Approved by Jose Angulo Apr 29, 2018

Gaurav Rawal<sup>1</sup>, grawal@iastate.edu; Jose Angulo<sup>2</sup>, jose.angulo@zoetis.com; Daniel C.L.

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133 score, level of viremia, duration of viremia and/or average daily gain (ADG)?

134 **Data collection process:**

135 Study level information

136 1. What is the study id?

137 2. What was the year of the publication?

138 3. What was the year of study conduct?

139 4. What was the country of trial?

- 140 5. Describe the Age and weight units at enrollment?
- 141 6. What was the gender composition?
- 142 7. What was breed or genetic line?
- 143 8. Number of groups in the design?
- 144 9. Pigs were challenged before or after vaccination?
- 145 10. Time from acquisition to vaccination(days)?
- 146 11. Number of days between vaccination and challenge?
- 147 12. Frequency of vaccination?
- 148 13. Vaccination route(s)?
- 149 14. Challenge route(s)?
- 150 15. Dose of challenge?
- 151 16. Which PRRSV strain was used as inoculum?
- 152 17. Report percentage genetic similarity of challenged strain with Foster vaccine strain?
- 153 18. Days between PRRSV challenge and necropsy?
- 154 19. What outcome was reported?
- 155 20. What is the next outcome you want to report?

156 Arm level information

- 157 1. Number of treatment groups?
- 158 2. What method was used for randomization?
- 159 3. How many pigs were allocated in Foster vaccinated and challenged group?
- 160 4. How many pigs were allocated in unvaccinated and challenged i.e. control group?
- 161 5. How many pigs were allocated in another group?
- 162 6. How many weeks of age, they were vaccinated?

- 163 7. What was the mean macroscopic lung lesion score in Fosterla vaccinated and challenged  
164 group?
- 165 8. What was the mean macroscopic lung lesion score in unvaccinated and challenged  
166 group?
- 167 9. What was the level of viremia in Fosterla vaccinated and challenged group?
- 168 10. What was the level of viremia in unvaccinated and challenged group?
- 169 11. What was the duration of viremia in Fosterla vaccinated and challenged group?
- 170 12. What was the duration of viremia in unvaccinated and challenged group?
- 171 13. What was the mean average daily weight gain in Fosterla vaccinated and challenged  
172 group?
- 173 14. What was the mean average daily weight gain in unvaccinated and challenged group?

#### 174 Data collection process

175 Data extraction will be completed independently by at least two reviewers from all eligible  
176 manuscripts. In the event, same study is obtained from multiple sources (i.e. conference  
177 proceedings and a manuscript from MEDLINE), the different sources will be combined to obtain  
178 the most complete trail description.

#### 179 Data items

#### 180 Source of heterogeneity

181 The source of heterogeneity will be PRRSV challenged strain as inoculum, age of pigs when  
182 they are purchased, source from where they are purchased, breed of pigs, weight of pig before  
183 the start of trial, number of days for acclimation before the start of trial, number of pigs per

184 group, number of groups, challenge dose, route of challenge, individually housed or group  
185 housed.

#### 186 Study level information

187 Country where study was conducted, year of conduct, pig mean age, mean weight, gender  
188 composition, breed or genetic line of pigs involved, duration of study observation period.

#### 189 Arm level information

190 Interventions used in each arm (PRRSV strain, dose, route, duration) total number of pigs in trial  
191 arm, number of events (high lung lesion score) in trial arm at the end of study period, mean lung  
192 lesion score outcome per trial arm, mean score of lung lesion score outcome per trial arm,  
193 pharmaceutical sponsorship of treatment, description of blinding of outcome assessment  
194 included (yes/no), description of use of randomization to group (yes/no), use of systematic  
195 allocation to treatment arm (yes/no), and use of allocation restrictions (blocking by time,  
196 blocking by weight, stratification by severity, stratification by sex).

#### 197 **Outcomes and prioritization**

198 The primary outcome of interest is mean score of macroscopic lung lesions, and secondary  
199 outcomes of interest are level of viremia, duration of viremia and average daily gain (ADG).

#### 200 **Risk of bias in individual studies**

201 The Cochrane Risk of Bias Scale for intervention studies will be used to assess bias for all  
202 outcomes together (macroscopic, magnitude and duration of viremia, and ADG) as these are all  
203 considered objective outcomes (Higgins et al., 2011). The bias domains include selection bias  
204 (sequence generation and allocation concealment), detection bias (outcome assessor blinding),



attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential sources of bias. Two reviewers will be independently assessing all sources of bias as “high risk”, “low risk”, or “unclear”. This information will be used as a source of heterogeneity in the meta-analysis.

## **Data Synthesis**

We propose to conduct a meta-analysis using a pair-wise comparison. The suitability of the dataset for this method will be determined when data has been extracted in consultation with a statistician. Unit of analysis will be handled by exclusion as all studies must have the individual as the unit of allocation. Studies with missing data will be excluded from the meta-analysis and identified as such in the results.

Subgroup analysis will include assessment of factors associated with methodological and clinical heterogeneity. The methodological factors (sponsorship and blinding) will be used to assess the systematic bias between studies where the null hypothesis is the beta estimates of the trial factors equal zero. We expect the potential sources of clinical heterogeneity to be the PRRSV strain, number of pigs per group, number of groups, challenge dose, route of challenge, calculation of outcomes, lung lesion evaluation DPC. We will assess this including these factors as indicator variables in the model where the null hypothesis is the beta estimates of the trial factors equal zero.

If quantitative synthesis is determined to be unfeasible, a systematic narrative synthesis paired with descriptive pairwise forest plots will be produced explaining the characteristics and findings within and between included studies.

## **Meta-bias(es)**

227 To assess publication bias, we will attempt use a selection model based on study size, study  
228 design, estimated effect size, and sponsorship to determine estimates of propensity for  
229 publication (Mavridis et al., 2014). Based on previous reviews, it is unclear how many different  
230 study designs (e.g. active-to-active, placebo-controlled trials, three arm trials) will be observed  
231 and thus publication bias will be difficult to ascertain.

#### 232 **Confidence in cumulative evidence**

233 We will summarize the data using the GRADE approach, with a summary of findings tables and  
234 evidence profiles for the multiple outcomes. All the outcomes are considered important or  
235 critical.